Long-Term Outcomes of 50 Cases of Limited-Resection Trial for Pulmonary Ground-Glass Opacity Nodules

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Introduction: From 1998 to 2002, we performed a trial of prospective limited resection for pulmonary ground-glass opacity lesions 2 cm or smaller. This is the second report on the long-term outcome.
Methods: The enrollment criteria of the trial were as follows: pulmonary peripheral nodule less than 2 cm, diagnosis or suspected diagnosis of clinical T1N0M0 carcinoma with ground-glass opacity and lack of evident pleural indentations or vascular convergence on high-resolution computed tomography. Limited-resection (wedge or segment) specimens were intraoperatively examined by frozen section. If the nodule was confirmed as Noguchi type A or B with a resection margin of greater than 1 cm, the incision was sutured and the patient followed up. The median surveillance period was 10 years.
Results: In a total of 50 enrolled participants, there were two Noguchi type A, 23 type B and 15 type C adenocarcinomas; five atypical adenomatous hyperplasias, four fibroses, and one granuloma. Although there were no patients with recurrence within the first 5 years, in four patients who underwent limited-resection pulmonary adenocarcinoma developed more than 5 years after the initial resection, of either cut-end recurrence or metachronous primary disease.
Conclusions: Of 26 patients who underwent limited resection, adenocarcinoma developed in four after more than 5 years. These were possibly cut-end recurrences. We concluded that 5 years is not a sufficient period for follow-up, and that limited resection should still be done only in a trial setting, even for small ground-glass opacity lesions.

Key Words: Lung cancer, Adenocarcinoma, Limited resection, Ground-glass opacity, Noguchi classification.

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In 2005, we reported the study design, methods, and preliminary results of our previous prospective trial on limited resection for pulmonary ground-glass opacity (GGO) nodules at the median follow-up point of 50 months.[1] At that time, 26 patients who had undergone limited resection (two for Noguchi type A, 23 for type B, and one for type C adenocarcinomas)[2] were free from recurrence. In those 26 patients, Noguchi type A and B lesions seemed to be in situ, noninvasive carcinomas, and we speculated that limited resection could be curative surgery for these diseases. In the trial, 14 patients with Noguchi type C lesions underwent lobectomy and lymph node dissection, and no nodal involvement, lymphatic permeation, or vascular invasion was observed. Therefore, we speculated that even patients with Noguchi type C lesions in our trial could also have been curatively treated by limited resection.

However, during continued long-term follow-up, in four of the 26 patients who underwent limited resection, pulmonary adenocarcinoma developed in areas surrounding the initial limited-resection cut-end staples more than 5 years after the initial surgery. We speculated that these might have been cut-end recurrences. We previously reported the details of three of these four patients in 2010 and warned of the possibility of late recurrence after limited resection, even for small GGO lesions.[3] With the median follow-up period of the patients enrolled in this trial having reached 10 years, we set out to determine the long-term recurrence rate of small GGO lung adenocarcinomas after limited resection.

PATIENTS AND METHODS

Patients

From 1998 to 2002, we enrolled 50 patients in this study.[1] Enrollment criteria were: tumor less than 2 cm in diameter, diagnosed as or suspected to be a clinical T1N0M0 carcinoma[4] in the lung periphery on computed tomography (CT); high-resolution CT findings suggestive of a Noguchi type A or B adenocarcinoma (i.e., GGO and lack of evident pleural indentation or vascular convergence). Patients with a history of malignancy within the previous 5 years and those who were not indicated for lobectomy and systematic lymph node dissection were excluded. Written informed consent was obtained from each participant. The study protocol was reviewed by the Institutional Review Board of the National Cancer Center Hospital East (Chiba, Japan) and was approved in July 1998.

We performed limited resection, wedge resection, or segmentectomy as appropriate. We performed segmentectomy when the nodule was located deep in the middle of a segment

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or could not be located intraoperatively. A frozen-section specimen was examined intraoperatively to identify Noguchi type A or B lesions, as described in detail in our previous report.[1] If the tumor was confirmed as Noguchi type A or B with a resection margin greater than 1 cm, the wound was closed and the patient followed up on an outpatient basis. If the resected margin was insufficient, an additional margin was resected. If the tumor was a primary malignancy, but not Noguchi type A or B lesions, lobectomy and systematic lymph node dissection were additionally performed. Patients were followed up on an outpatient basis at a minimum of every 6 months by physical check-up, plain chest radiography, and laboratory testing. Patients who underwent limited resection for Noguchi type A or B lesions had chest CT scans taken every year.

Of the 36 patients who were given intraoperative diagnoses of Noguchi type A or B tumors or nonmalignancy, 30 underwent wedge resection and six underwent segmentectomy. We performed lobectomy and lymph node dissection in 14 patients with intraoperative diagnoses of type C tumors. The final pathologic diagnosis of 50 cases was 40 adenocarcinomas, including two Noguchi type A, 23 type B, and 15 type C tumors, five atypical adenomatous hyperplasias, four fibroses, and one granuloma.[1]

Statistical Analysis

The primary endpoint for analyses was the recurrence-free proportion of patients, measured from the date of surgery to the date when possible recurrence was suspected for the first time. The last follow-up observation was censored when the patient was alive without any signs of recurrence, was lost to follow-up, or died from any cause other than lung cancer. We also measured overall survival from the date of surgery to the date of death from any cause. The recurrence-free proportion curve was plotted using the Kaplan–Meier method and the statistical significances of difference between the subgroups were determined by the two-sided log-rank test. A p value of less than 0.05 was considered to represent a statistically significant difference. We used statistical analysis software, Dr. SPSS II for Windows, Standard Version 11.0 (SPSS Inc., Chicago, IL) for all analyses.

RESULTS

Long-Term Outcome Among 40 Adenocarcinoma Patients

After the preliminary results were published, we continued to observe the 40 adenocarcinoma patients with a median follow-up period of 10 years. There were no patients with recurrence within the first 5 years. However, in four patients who had undergone limited resection, pulmonary adenocarcinoma developed in the area surrounding the cut-end staples of the initial limited resection 5 years or later after the initial surgery. Of these, three had Noguchi type B tumors, and one had a type C tumor, which was initially diagnosed as type B by frozen-section examination. Therefore, this patient only underwent wedge resection. After detailed discussion, he decided not to have any further treatment on his own will. All the other 14 type C patients who underwent lobectomy and lymph node dissection are free from recurrence or metachronous primary disease at the time of writing (Fig. 1).

The characteristics of the four patients in whom pulmonary adenocarcinoma developed around the area of the cut-end scar are shown in the Table 1. All of them initially underwent wedge resection, and had intraoperative frozen-section diagnoses of Noguchi type B. We reported the findings in patients No. 1 to 3 in detail previously.[3] Solid nodular shadows appeared at the cut-ends of initial limited-resection sites, more than 5 years after the initial surgery in all four patients. These secondary lesions were cytohistologically diagnosed as adenocarcinomas, and they showed the same epidermal growth factor receptor mutation status as the primary lesions in three of the four patients. Therefore, we diagnosed them to be possible cut-end recurrences rather than metachronous primary diseases.

Figure 2*A* shows the recurrence-free proportion curve of the 40 adenocarcinoma patients. The 5- and 10-year recurrence-free proportions were 100% and 92%, respectively. There was one patient who died from lung cancer and one who died from other malignant disease. The overall 5- and 10-year survival rates were 100% and 95%, respectively. Figure 2*B* shows the recurrence-free proportion curve of the 26 patients who underwent limited resection, in comparison with that of the 14 patients who underwent lobectomy. The 5- and 10-year recurrence-free proportions of the limited-resection patients were 100% and 87%, respectively. There were no statistically

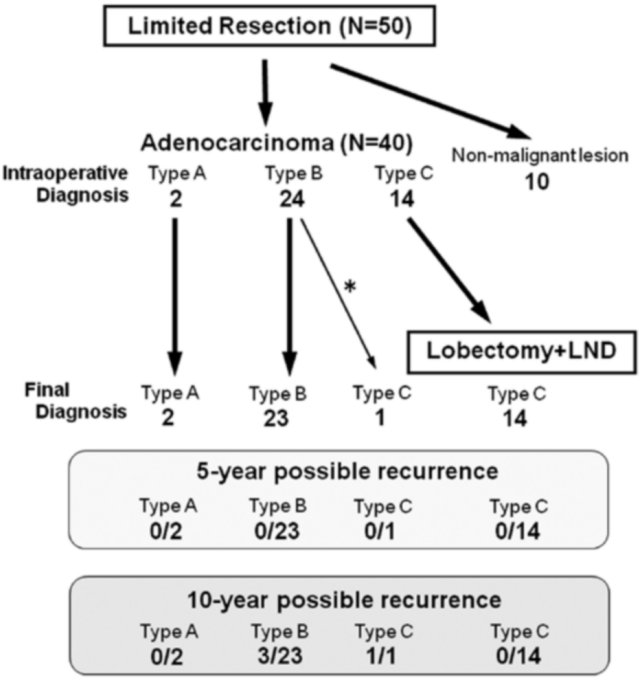

FIGURE 1. The intraoperative and final pathologic diagnosis, operative procedure, and long-term outcome of 40 adenocarcinoma patients; 1 patient had a type C tumor which was intraoperatively diagnosed as type B by frozen-section examination, and this patient underwent wedge resection only (asterisk). LND, lymph node dissection.

TABLE 1. Characteristics of Four Patients with Possible Recurrence

No.	Size (mm)	Final Diagnosis	Site of Initial Recurrence	Time to Recurrence (Yrs)	Status of EGFR Mutation Primary / Recurrence	Treatment for Recurrence	Outcome (Yrs)
1.	20	Type B	Cut-end scar	7.9	L858R and S768I/L858R	Reoperation	Alive (11.6)
2.	11	Type B	Cut-end scar	5.5	E746-A750 del type 2/E746-A750 del type 2	Reoperation	Alive (9.8)
3.	20	Type C	Cut-end scar and pleural effusion	8.0	None/none	EGFR-TKI	Dead (9.0)
4.	15	Type B	Cut-end scar and contralateral lung	10.5	L858R/L858R	EGFR-TKI	Alive (12.1)

EFGR, epidermal growth factor receptor. TKI, tyrosine-kinase inhibitor.

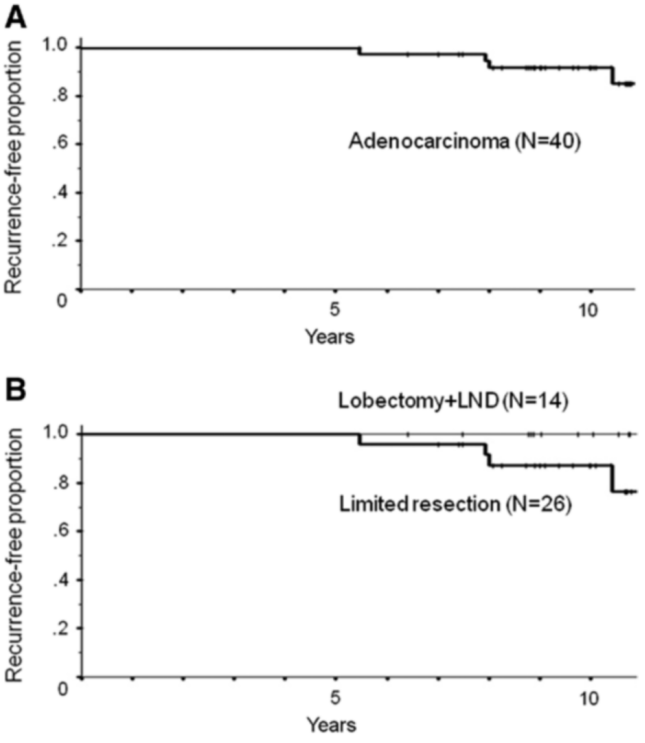

FIGURE 2. ***A***, The recurrence-free proportion curves of 40 adenocarcinoma patients, and (***B***) 26 patients who underwent limited resection, in comparison with 14 patients who underwent lobectomy. LND, lymph node dissection.

significant differences in recurrence-free proportion between the limited resection and lobectomy groups ($p = 0.136$).

DISCUSSION

During the monitoring of the patients who had undergone limited resection (median follow-up period, 10 years), three patients with Noguchi type B and one with Noguchi type C tumors at the final pathologic diagnosis developed pulmonary adenocarcinoma 5 years or more after limited resection. In all cases, the second cancers developed in the areas surrounding the initial limited-resection cut-end staples, which strongly suggests they were cut-end recurrences rather than metachronous primary cancer. However, in one of the four patients, the second cancer harbored only one of the two point mutations observed in the *EGFR* gene of the first cancer, and therefore we strongly speculate that this second cancer was a metachronous primary lesion.[3] Regardless of the etiology, the disease-control rate of the limited resection in our trial was unacceptably low, at 85% (22 of 26). The minimum resection margin of greater than 1 cm in our trial setting may have been insufficient to completely remove cancer cells by limited resection.

Surgical resection was not indicated in two of the four patients because their second cancer in these areas had already disseminated into the thoracic cavity upon detection. Although there were no statistically significant differences in recurrence-free proportion between the limited resection and lobectomy groups in the current series, this lack of significance have been caused by a beta error. All 14 patients with invasive type C adenocarcinoma who underwent standard lobectomy and lymph node dissection remain free from recurrence or metachronous cancer at the time of writing this article. Lobectomy might be the curative treatment of choice even for small GGO adenocarcinomas. Care must be taken in determining the indication for limited resection, which should be assessed further in a trial setting.

The most notable result in the present study is the length of time to recurrence. In our first report, we suggested that a 5-year follow-up period is insufficient to conclude that the disease is cured, considering the probable slow-growing nature of GGO lesions, and that an additional 5 years of monitoring is necessary to yield definitive conclusions.[1] We previously described the considerable risk of the late recurrence of non–small-cell lung cancer more than 5 years after curative surgery.[5,6] These findings prompted us to continue to follow-up of limited-resection patients in whom we observed possible cut-end recurrence 5 years or more after limited resection. There are several prospective studies of limited resection for pulmonary adenocarcinoma reported from Japan.[7–10] In these studies, wedge resection was performed mostly for intraoperatively diagnosed noninvasive adenocarcinomas, and no recurrences or cancer-related deaths were observed. However, these results were obtained after a relatively short median follow-up period of 29 to 51 months, which may have been insufficient to determine these slow-growing cancers as cured.

In Japan, a single-arm, limited-resection trial, Japanese Clinical Oncology Group (JCOG) 0804/West Japan Oncology Group (WJOG) 4507L is ongoing for subsolid T1aN0M0[11] peripheral tumors with a consolidation–tumor size ratio of 0.25 or less. A total of 330 patients had been enrolled as of April 2011, and therefore the 10-year follow-up results will not be available until 2020. Another two major randomized, limited-resection trials, JCOG0802 / WJOG4607L and Cancer

and Leukemia Group B-140503, are still in the accumulation phase in Japan and in the United States and Canada, respectively. Their aims are to compare limited resection with standard lobectomy for T1aN0M0 peripheral non–small-cell lung cancer. These are ambitious projects that could raise the standard of lung cancer surgery. However, considering the possibility of delayed cut-end recurrence, clinicians should refrain from indicating limited resection in clinical practice until the abovementioned trials clearly show that limited resection is the treatment of choice for these types of small lung cancer. Currently at our department, for a subsolid T1aN0M0 peripheral tumor with a consolidation–tumor size ratio of 0.25 or less, we indicate limited resection only when the patient's consent is obtained after discussion based on our in-house and JCOG0804/ WJOG4507L limited-resection experiences. For a tumor with a consolidation–tumor size ratio of greater than 0.25, we ask the patient to participate in JCOG0802 / WJOG4607L trial. If the patient agrees to participate, he or she is randomly allocated to segmentectomy or lobectomy. If not, we indicate standard lobectomy and node dissection.

CONCLUSIONS

To the best of our knowledge, this is the first report in the literature on the long-term outcome of a prospective limited-resection trial of pulmonary small GGO lesions after a median follow-up period of 10 years. The findings of four possible cases of delayed cut-end recurrence clearly demonstrate the need for long-term follow-up of more than 5 years, and that limited resection should still be done only in a trial setting, even for small GGO cancer.

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REFERENCES

1. Yoshida J, Nagai K, Yokose T, et al. Limited resection trial for pulmonary ground-glass opacity nodules: fifty-case experience. *J Thorac Cardiovasc Surg* 2005;129:991–996.
2. Noguchi M, Morikawa A, Kawasaki M, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. *Cancer* 1995;75: 2844–2852.
3. Yoshida J, Ishii G, Yokose T, et al. Possible delayed cut-end recurrence after limited resection for ground-glass opacity adenocarcinoma, intraoperatively diagnosed as Noguchi type B, in three patients. *J Thorac Oncol* 2010;5:546–550.
4. Sobin LH, Wittekind C. TNM Classification of Malignant Tumours, 6th Ed. New York: Wiley-Liss, 2002.
5. Maeda R, Yoshida J, Hishida T, et al. Late recurrence of non-small cell lung cancer more than 5 years after complete resection: incidence and clinical implications in patient follow-up. *Chest* 2010;138:145–150.
6. Maeda R, Yoshida J, Ishii G, et al. Long-term outcome and late recurrence in patients with completely resected stage IA non-small cell lung cancer. *J Thorac Oncol* 2010;5:1246–1250.
7. Yamato Y, Tsuchida M, Watanabe T, et al. Early results of a prospective study of limited resection for bronchioloalveolar adenocarcinoma of the lung. *Ann Thorac Surg* 2001;71:971–974.
8. Yamada S, Kohno T. Video-assisted thoracic surgery for pure ground-glass opacities 2 cm or less in diameter. *Ann Thorac Surg* 2004;77: 1911–1915.
9. Watanabe T, Okada A, Imakiire T, Koike T, Hirono T. Intentional limited resection for small peripheral lung cancer based on intraoperative pathologic exploration. *Jpn J Thorac Cardiovasc Surg* 2005;53:29–35.
10. Koike T, Togashi K, Shirato T, et al. Limited resection for noninvasive bronchioloalveolar carcinoma diagnosed by intraoperative pathologic examination. *Ann Thorac Surg* 2009;88:1106–1111.
11. Goldstraw P. *An International Association for the Study of Lung Cancer: IASLC Staging Manual in Thoracic Oncology,* Orange Park, FL: Editorial Rx Press, 2009.